transmembrane domain, and require a cell membrane comprising (i) a polypeptide comprising an LDL receptor transmembrane domain fused to a C-terminal tail, and (ii) a protease which specifically cleaves the domain and thereby releases the tail from the membrane. In contrast, Willnow describes an LRP which is cleaved at an N-terminal, extracellular site, and the protease does not and cannot release from the membrane any C-terminal tail.

The Examiner correctly observes that Willnow et al. describe using an anti-LRP antibody directed against the cytoplasmic tail of LRP to identify unprocessed precursor (region IV) and the processed 85-kDa carboxyl-terminal fragment (Fig 2; para. bridging p.15828-15829) on immunoblots made from extracted and partially purified membrane proteins. Accordingly, in Willnow the carboxyl-terminal fragment is released from the membrane not by the protease, but rather by subsequent biochemical extraction. In Willnow, protease cleavage at the N-terminal, extracellular region IV processing site yields a membrane-bound fragment. The membrane-bound C-terminal cleavage produce is then biochemically extracted from the membrane. In contrast, our claims require that cleavage by the protease release the tail from the membrane, which does not and cannot occur in Willnow's work.

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Willnow has been described above. Herz (2001, Neuron 29, 571-81) describes LDL receptor family proteins, and reviews the diverse physiological roles that these receptors have been found to play. However, nowhere does Herz disclose or suggest producing and detecting a protease liberated C-terminal tail of any LDR receptor as required by our claims.

Claim Construction

There appears to be no dispute that the disclosed invention is patentable over the cited art, but only whether a critical feature of the invention (cleavage at intramembrane or cytoplasmic sites) is recited in the claims (e.g. Advisory Action, p.5, lines 1 - 15). The Action construes the claims to merely require "a protease that cleaves a domain and releases a tail from the membrane." Advisory Action, p.5, lines 1–18. However, this quotation strategically omits a critical word from our claim, eliminating a required causality, and effectively changing the substance of the claimed invention.

Steps (b) and (c) of claim 1 read as follows:

b) incubating the sample under conditions wherein the protease cleaves the domain and thereby releases the tail from the membrane; and

c) detecting a resultant released tail, which indicates proteolysis of the LDL receptor transmembrane domain.

Note that "the protease cleaves the domain and *thereby* releases the tail from the membrane". The claim expressly and affirmatively *requires* that release of the tail result from the protease cleavage. If cleavage does not effect release of the tail, but rather the tail is released by some independent mechanism, such as biochemical extraction, our claim is not infringed. This requirement is furthered in step (c) wherein the "*resultant* released tail" is detected – not any released tail, but only a tail released as a result of the protease cleavage recited in step (b), and not a tail released as a result of some independent mechanism, such as biochemical extraction.

Even if the causality requirement of our claim was relegated to a terminal "whereby clause", it still could not be properly disregarded ("when the "whereby" clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention. Hoffer v. Microsoft Corp., Case No. 04-1103 (Fed. Cir. Apr. 22, 2005)). In our case however, the causality limitation is an inextractable requirement of expressly and affirmatively recited method steps (b) and (c).

Of course, Applicants will be pleased to provide or approve any equivalent claim language preferred by the Examiner that similarly requires that the release of the tail result from the recited protease cleavage, such as the following proposed amended version of claim 1:

1. (Proposed Amendment) A method for detecting proteolysis of an LDL (Low Density Lipoprotein) receptor transmembrane domain, comprising the steps of:

a) providing a sample comprising a cell membrane comprising (i) a polypeptide comprising an LDL receptor transmembrane domain fused to a C-terminal tail, and (ii) a protease which specifically cleaves the domain and thereby releases the tail from the membrane;

b) incubating the sample under conditions wherein the protease cleaves the domain ~~and thereby~~ which releases the tail from the membrane; and

c) detecting a resultant released tail, which indicates proteolysis of the LDL receptor transmembrane domain.

The Examiner is invited to call the undersigned if she would like to amend the claims to clarify the foregoing or seeks further clarification of the claim language.

We petition for and authorize charging our Deposit Account No.19-0750 all necessary extensions of time. The Commissioner is authorized to charge any fees or credit any overcharges relating to this communication to our Dep. Acct. No.19-0750 (order UTSD:0862).

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP

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